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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference SN-44 | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/JP 01/03377 | International filing date (day/month/year) 20/04/2001 | (Earliest) Priority Date (day/month/year) 21/04/2000 |
| Applicant SUNTORY LIMITED et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

SUBSTITUTED 1-AZA-2-IMINO-HETEROCYCLES AND THEIR USE AS NICOTINIC ACETYLCHOLINE RECEPTORS ACTIVATORS

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 3-9

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the above mentioned claims.

The search and the report for those claims can only be considered complete for the subject-matter as recited in claim 2, i.e. the examples of the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 01/03377

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D277/18 C07D277/40 C07D401/06 C07D417/06 C07D213/73
C07D233/88 C07D403/06 A61K31/426 A61K31/427 A61K31/505
A61K31/506 A61K31/4164 A61K31/4178 A61K31/44 A61K31/4427

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | MEAKINS G D ET AL: "Substituted imidazo'2,1-b!thiazoles from 2-aminothiazoles and alpha-bromo ketones: efficient preparation and proof of structure" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, no. 3, March 1989 (1989-03), pages 643-648, XP002178318 page 644, scheme 1, compounds (3) and (4) --- | 1,2 |
| X | US 3 274 209 A (RAEYMAEKERS A H M ET AL) 20 September 1966 (1966-09-20) example 43 --- | 1,2 |
| X | US 5 212 192 A (RAEYMAEKERS A H M ET AL) 18 May 1993 (1993-05-18) tables 1-4 --- | 1 |
| | --- -/-- | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

Date of the actual completion of the international search

25 September 2001

Date of mailing of the international search report

09/10/2001

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 01/03377

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | YALE H L ET AL: "1-Aralkyl-2(1H)pyridinimines and their derivatives" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 12, no. 5, October 1975 (1975-10), pages 1027-1029, XP002178319 the whole document --- | 1 |
| X | JEN T ET AL: "Amidines. 4. Synthesis of tricyclic guanidines related to 1,2,3,5-tetrahydroimidazo(2,1-b)quinazoline, a new antihypertensive agent" JOURNAL OF MEDICINAL CHEMISTRY, vol. 16, no. 4, 1973, pages 407-411, XP002134186 the whole document --- -/-- | 1 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

25 September 2001

Date of mailing of the international search report

Name and mailing address of the ISA

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Allard, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 01/03377

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 01/03377

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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|------------|---|-----------------------|
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Information on patent family members

International Application No

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International Application No

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31/4427, A61P 25/28

16-16, Dai-cho, Ashikaga-shi, Tochigi 326-0056 (JP).
AKABANE, Minako [JP/JP]; 1-37-201, Sojiji 1-chome,
Ibaraki-shi, Osaka 567-0801 (JP). **TANI, Yoshihir**
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(JP).

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(81) Designated States (*national*): AU, CA, CN, KR, US.

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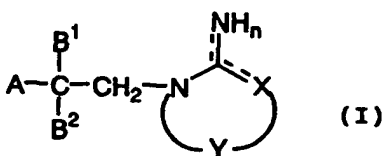
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(72) Inventors; and

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Gunma 374-0029 (JP). **IWANAMI, Tatsuya** [JP/JP];

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: SUBSTITUTED 1-AZA-2-IMINO-HETEROCYCLES AND THEIR USE AS NICOTINIC ACETYLCHOLINE RE-
CEPTORS ACTIVATORS



(57) Abstract: There is provided heterocyclic compounds of the following formula (I): in which, A is optionally substituted alkyl group, optionally substituted aryl group or optionally substituted heterocyclic group; B¹ and B² are, hydrogen atom, alkyl group or hydroxyl group; or combined together to represent carbonyl group; X is oxygen atom, sulfur atom, carbon atom or nitrogen atom; dotted line shows either presence or absence of bond; n is integer of 1 or 2; and the group -X-Y- represents optionally substituted alkylene or cyclic alkenylene bond; or a pharmaceutically ac-
ceptable salt thereof. These compounds have good affinity for $\alpha 4\beta 2$ nicotinic acetylcholine receptors and activate the same to thereby exert a preventive or therapeutic effect on cerebral dysfunction.11

WO 01/81326 A1

DESCRIPTION

SUBSTITUTED 1-AZA-2-IMINO-HETEROCYCLES AND THEIR USE AS NICOTINIC ACETYLCHOLINE RECEPTORS ACTIVATORS

5 TECHNICAL FIELD

The present invention relates to compounds showing affinity for nicotinic acetylcholine receptors and activating the same. The compounds of the present invention are useful for preventing or treating of neurodegenerative diseases such as
10 Alzheimer's disease and Parkinson's disease, dementia such as cerebrovascular dementia, motor ataxia such as Tourette's syndrome, neurosis during chronic cerebral infarction stage, neuropathy and mental disorder such as anxiety and schizophrenia and cerebral dysfunction caused by cerebral injury.

15

BACKGROUND ART

It has been widely known that nicotine exerts a wide variety of pharmacological effects. These include, for example, cholinergic nervous activation as the effect on central nervous
20 systems such as facilitation of acetylcholine release [De sarno P. & Giacobini E., *J. Neurosci. Res.*, 22, 194-200 (1984)], and further, activation effect on monoaminergic nervous systems [Levin E. D. & Simon B. B., *Psychopharmacology*, 138, 217-230 (1998)].

25

It has been also reported that nicotine possesses lots of very useful cerebral function improving effects such as increasing cerebral blood flow and glucose uptake rate in brain [Decker M. W. et al., *Life Sci.*, 56, 545-570 (1995)].

It has been further reported that nicotine inhibits
30 amyloid formation of β -peptides which is believed to be the cause of neuronal cell death during Alzheimer's disease [Salomon A. R. et al., *Biochemistry*, 35, 13568-13578 (1996)], and have cell

protective effects on neuronal cell death induced by β -amyloid (A β) [Kihara T. et al., *Ann. Neurol.*, 42, 156-163 (1997)]. Recent studies suggest the possibility of nicotine being a remedy for the inflammatory colitis [Sandborn W. J. et al., *Ann. Intern. Med.*, 126, 364 (1997)].

On the other hand, it is acknowledged that in the patients of Alzheimer's disease, the degeneration of acetylcholinergic neurons known to be one of the important nervous systems responsible for cognition such as attention, learning, memory and recognition, is altered and thus nicotinic acetylcholine receptors in the cerebral cortex and hippocampus are drastically decreased [Nordberg A. et al., *J. Neurosci. Res.*, 31, 103-111 (1992)].

It is reported the possibility of the useful treatment for Alzheimer's disease by activating nicotinic acetylcholine receptors to be recovered the acetylcholine nervous systems mechanism by agonists or modulators of nicotinic acetylcholine receptors [Newhouse P. A. et al., *Psychopharmacology*, 95, 171-175 (1988)].

The nicotinic acetylcholine receptors belong to the ion channel neurotransmitter receptors composed of five subunits. That is, agonists such as acetylcholine, nicotine and the like are bound to receptors to activate and open the channels thereof, thus causing the influx of cationic ion such as sodium ion from extracellular to result the cell excitation [Galzi J. L. & Changeux J. P., *Neuropharmacology*, 34, 563-582 (1995)]. The aforementioned agonists such as acetylcholine, nicotine and the like show its effect by binding to the specific site existing in α subunit so-called agonist binding site.

It is known, on the other hand, that compounds such as galantamine and so on which activate cells by potentiating the effects of acetylcholine, have no agonist effect at nicotinic

acetylcholine receptors directly. These compounds show their effects through allosteric site which is clearly different from the agonist binding sites [Schrattenholz A. et al., *Mol. Pharmacol.*, 49, 1-6 (1996)].

5 Mentioned above, compounds capable to activate nicotinic acetylcholine receptors indirectly are called modulators and it is expected to be the practical medicines for treatment of the various neurological diseases [Lin N. -H & Meyer M. D., *Exp. Opin. Ther. Patents*, 8, 991-1015 (1998)].

10 The terms "agonists" and "modulators" are used in these definitions in the present specification.

 The nicotinic acetylcholine receptors are believed to participate not only in Alzheimer's disease, but also in neurodegenerative diseases such as Parkinson's disease, and many
15 of the neuroses and psychoses such as dementia, anxiety, schizophrenia and so on [Barrantes F. J., in *The Nicotinic Acetylcholine Receptor*, ed. Barrantes F. J., Springer, 1997, p175-212; Lena C. & Changeux J. -P., *J. Physiol. (Paris)*, 92, 63-74 (1998)].

20 Especially, since it is known that cerebral blood flow of the patients suffering from cerebrovascular dementia caused by cerebral infarction is decreased [Takagi Shigeharu, *Gendai Iryo*, 28, 1157-1160 (1996); Tachibana H. et al., *J. Gerontol.*, 39, 415-423 (1984)], there seems to be the possibility of agonists of
25 nicotinic acetylcholine receptors or the modulators possessing cerebral blood flow increasing effect to be applied to the medicines in this area of treatment. Furthermore, recent study revealed that agonists of nicotinic acetylcholine receptors and the modulators thereof show analgesic activities [Bannon A. W. et
30 al., *Science*, 279, 77-81 (1998)].

 Nicotine itself surely affects as the agonist of nicotinic acetylcholine receptors. For example, after administration of

nicotine to the patients of Alzheimer's disease, the recoveries of their attention or the short-term memory were observed, and also the symptoms of their disease were improved [Newhouse P. A. et al., *Drugs & Aging*, 11, 206-228 (1997)]. Nevertheless, nicotine also possesses disadvantages such as widely recognized addiction, as well as low bioavailability and severe side effects to the cardiovascular systems.

Therefore, there have been great expectation to develop nicotinic acetylcholine receptors agonists or modulators as medicines in place of nicotine which has no addiction, high bioavailability, and less side effects on cardiovascular systems [Maelicke A. & Albuquerque E. X., *Drug Discovery Today*, 1, 53-59 (1996); Holladay M. W. et al., *J. Med. Chem.*, 40, 4169-4194 (1997)].

There are some subtypes known as the nicotinic acetylcholine receptors [Shacka J. J. & Robinson S. E. T., *Med. Chem. Res.*, 1996, 444-464], and mainly $\alpha 4\beta 2$ subtype receptors exist in central nervous systems. Furthermore, there exist $\alpha 1\beta 1\gamma\delta$ (or $\alpha 1\beta 1\delta$) subtype receptors in the neuromuscular junction of motor neurons, and $\alpha 3\beta 4$ subtype receptors in ganglion of autonomic nervous systems and adrenal.

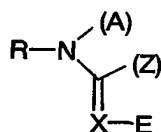
The activation of the cholinergic nervous systems and increasing effect of cerebral blood flow are believed to occur though $\alpha 4\beta 2$ subtype receptors in central nervous systems, and above mentioned effects of nicotine on cardiovascular system are induced by affecting receptor subtypes exist in peripheral nervous system.

Therefore, it may be extremely useful as medicines having no side effects to develop compounds which have no affinity at $\alpha 1\beta 1\gamma\delta$ subtype nor $\alpha 3\beta 4$ subtype receptors, but selectively affects $\alpha 4\beta 2$ subtype receptors.

In these circumstances, there have been many proposals to

develop selective agonists or modulators at nicotinic acetylcholine receptors of central nervous system as practical medicines. These include, for example, the compound such as ABT-418 [Arneric S. P. et al., *J. Pharmacol. Exp. Ther.*, 270, 310-318 (1994); Decker M. W. et al., *J. Pharmacol. Exp. Ther.*, 270, 319-328 (1994)], ABT-089 [Sullivan J. P. et al., *J. Pharmacol. Exp. Ther.*, 283, 235-246 (1997); Decker M. W. et al., *J. Pharmacol. Exp. Ther.*, 283, 247-258 (1997)], GTS-21 [Arendash G. W. et al., *Brain Res.*, 674, 252-259 (1995); Briggs C. A. et al., *Pharmacol. Biochem. Behav.*, 57, 231-241 (1997)], RJR-2403 [Bencherif M. et al., *J. Pharmacol. Exp. Ther.*, 279, 1413-1421 (1996); Lippiello P. M. et al., *J. Pharmacol. Exp. Ther.*, 279, 1422-1429 (1996)], SIB-1508Y [Cosford N. D. P. et al., *J. Med. Chem.*, 39, 3235-3237 (1996); Lloyd. G. K. et al., *Life Sci.*, 62, 1601-1606 (1995)], SIB-1553A [Lloyd. G. K. et al., *Life Sci.*, 62, 1601-1606 (1995)] and so on.

In European Patent Publication EP679397-A2, substituted amine derivatives represented by the following formula were proposed for the medicines for prevention and treatment of cerebral dysfunction.



in which,

R represents hydrogen, optionally substituted acyl, alkyl, aryl, aralkyl, heteroaryl or heteroarylalkyl radicals;

A represents a monofunctional group of the hydrogen, acyl, alkyl or aryl series or represents a bifunctional group which is linked to the radical Z;

E represents an electron-withdrawing radical;

X represents the -CH= or =N- radicals, it being possible for the -CH= radical to be linked to the Z radical

instead of an H atom;

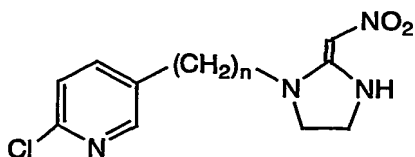
Z represents a monofunctional group of the alkyl, -O-R, -S-R or -NR₂ series or represents a bifunctional group which is linked to the A radical or the X radical.

5

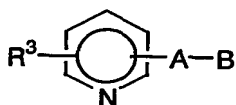
However, in the compounds disclosed in said patent publication, the E radical is restricted to the electron-withdrawing radical, and therefore, these compounds are clearly different from the compounds disclosed by the present patent application. Furthermore, there is no description in the above-mentioned patent publication that these compounds can selectively activate $\alpha 4\beta 2$ nicotinic acetylcholine receptors.

On the other hand, "imidacloprid", as a pesticide, is known to have the similar skeleton as the compounds of the present invention. It is confirmed that the imidacloprid electrophysiologically affects as partial agonist at nicotinic acetylcholine receptors of PC12 cell [Nagata K. et al., *J. Pharmacol. Exp. Ther.*, 285, 731-738 (1998)], and imidacloprid itself or its metabolites and their analogues possess affinity to the nicotinic acetylcholine receptors in mouse brain [Lee Chao S. & Casida E., *Pestic. Biochem. Physiol.*, 58, 77-88 (1997); Tomizawa T. & Casida J. E., *J. Pharmacol.*, 127, 115-122 (1999); Latli B. et al., *J. Med. Chem.*, 42, 2227-2234 (1999)], however, there is no report of the imidacloprid derivatives selectively activating $\alpha 4\beta 2$ nicotinic acetylcholine receptors.

Furthermore, among the nitromethylene type pesticides, the following compounds were synthesized to optimize the carbon chain length (n=0 to 3) between 6-chloro-3-pyridyl group and nitromethylene imidazoline group, and it was reported that insecticidal activities of the compound in which n is 2 was weaker than the compound in which n is 1 (Nishimura K. et al., *Pestic. Biochem. Physiol.*, 50, 51-59 (1994)).



Japanese Laid-open Patent Publication Number Hei 10-226684 disclosed [N-(pyridinylmethyl)heterocyclic]ylideneamine compounds represented by the following formula, pharmaceutically acceptable salts and prodrugs thereof.

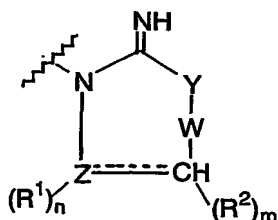


in which,

A represents the $-\text{CH}(\text{R})-$;

10 R^3 represents a hydrogen atom or an optionally substituted C_1 - C_6 alkyl; and

B represents the group of the following formula:



Nevertheless, among the compounds disclosed in said patent publication, the radical "A" which connects substituted pyridine ring and the radical "B", is substituted methylene group represented by $-\text{CH}(\text{R})-$, and therefore, these compounds are clearly different from the compounds of the present invention in which the linkage is composed of substituted ethylene bridge. It is disclosed that aforementioned compounds possess weak affinity to nicotinic receptors; however, there is no disclosure that these compounds have selective activating effect at $\alpha 4\beta 2$ nicotinic acetylcholine receptors of central nervous systems and

act as agonists or modulators of nicotinic acetylcholine receptors.

As mentioned above, there had been many attempts to develop agonists or modulators selectively activating $\alpha 4\beta 2$ nicotinic acetylcholine receptors of central nervous systems via oral administration, but none were satisfactory.

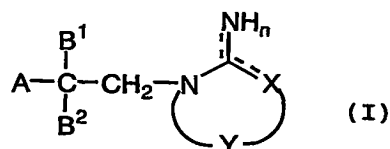
DISCLOSURE OF THE INVENTION

Therefore, the present invention provides therapeutic or preventing agents for treatment of diseases which may be prevented or cured by activating nicotinic acetylcholine receptors, having the capabilities of binding selectively with $\alpha 4\beta 2$ nicotinic acetylcholine receptor of central nervous systems, and having no undesirable side effects in cardiovascular systems such as hypertension or tachycardia.

More specifically, the present invention provides medicaments for preventing or treating various diseases, which may be prevented or cured by activating nicotinic acetylcholine receptors, such as dementia, senile dementia, presenile dementia, Alzheimer's disease, Parkinson's disease, cerebrovascular dementia, AIDS-related dementia, dementia in Down's syndrome, Tourette's syndrome, neurosis during chronic cerebral infarction stage, cerebral dysfunction caused by cerebral injury, anxiety, schizophrenia, depression, Huntington's disease, pain and so on.

Through extensive investigations of researching compounds having the capabilities of binding selectively with $\alpha 4\beta 2$ nicotinic acetylcholine receptors of central nervous systems, the present inventors discovered that the compounds represented by the formula (I) mentioned below and pharmaceutically acceptable salts thereof possess high affinity for nicotinic acetylcholine receptors in central nervous systems, and activate said receptors as agonists or modulators.

Accordingly, as one aspect of the present invention, it is provided heterocyclic compounds represented by the following formula (I):



5 wherein:

A is optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group;

10 B^1 and B^2 are, hydrogen atom; alkyl group; or hydroxyl group; or combined together to represent carbonyl group;

X is oxygen atom; sulfur atom; carbon atom; or nitrogen atom;

dotted line shows either presence or absence of bond;

n is integer of 1 or 2; and

15 Y is,

(1) in the case of X is oxygen atom, group -Y-X- is -CH₂-CH₂-O- or -CH₂-CH₂-CH₂-O-;

(2) in the case of X is sulfur atom, group -Y-X- is -CH₂-CH₂-S- or -C(R¹)=C(R²)-S- (in which, R¹ and R² are hydrogen atom; halogen atom; optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group);

(3) in the case of X is carbon atom, group -Y-X- is -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH=C(R³)-C(R⁴)=CH- or -N=C(R⁵)-C(R⁶)=CH- (in which, R³, R⁴, R⁵ and R⁶ are hydrogen atom; halogen atom; optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group); and,

(4) in the case of X is nitrogen atom, group -Y-X- is -CH₂-CH₂-NH-, -CH₂-CH₂-CH₂-NH-, -C(R⁷)=C(R⁸)-N=, or -C(R⁹)=C(R¹⁰)-C(R¹¹)=N- (in which, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are hydrogen atom;

halogen atom; optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group);

or pharmaceutically acceptable salts thereof.

5

Still another aspect of the present invention, it is provided activator agents for $\alpha 4\beta 2$ nicotinic acetylcholine receptors containing heterocyclic compounds of the formula (I) or pharmaceutically acceptable salt thereof as active ingredients.

10

As still further aspect of the present invention, it is provided that the use of heterocyclic compounds of the formula (I) or pharmaceutically acceptable salt thereof for treating or preventing of cerebral circulation disease, neurodegenerative disease and the like.

15

BEST MODE FOR CARRYING OUT THE INVENTION

Examples of the pharmaceutically acceptable salt include an inorganic acid salt such as hydrochloric acid salt, hydrobromic acid salt, sulfuric acid salt, phosphoric acid salt and the like, and an organic acid salt such as fumaric acid salt, maleic acid salt, oxalic acid salt, citric acid salt, tartaric acid salt, malic acid salt, lactic acid salt, succinic acid salt, benzoic acid salt, methanesulfonic acid salt, p-toluenesulfonic acid salt and the like.

25

The group represented by "A" in the compound of formula (I) is optionally substituted alkyl group, optionally substituted aryl group or optionally substituted heterocyclic group, and preferable examples of said optionally substituted alkyl group includes methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and the like.

30

The preferable examples of aryl group may include phenyl, naphthyl and the like. Suitable substituent of substituted aryl

group may include C₁-C₄ lower alkyl, hydroxyl group, alkylthio group, arylthio group, halogen atom and the like, and therefore, examples of said substituted aryl group include methylphenyl, hydroxyphenyl, (methoxyphenyl)thiophenyl, (hydroxyphenyl)thio-
5 phenyl, chlorophenyl, dichlorophenyl and the like.

The term "heterocyclic group" represented by "A" may be 5 or 6 membered heterocyclic group or condensed heterocyclic group thereof containing the same or different 1 to 3 hetero atom(s) such as sulfur, nitrogen, oxygen atom(s), and examples include
10 thiophene, furan, pyran, pyrrole, pyrazole, pyridine, pyrimidine, pyrazine, pyridazine, imidazole, oxazole, isoxazole, thiazole, isothiazole, quinoline, isoquinoline, indole, azaindole, tetrahydropyrimidine and the like.

Suitable substituent of substituted heterocyclic group may
15 include C₁-C₄ lower alkyl, halogen atom and the like, and therefore, examples of said substituted heterocyclic group may be 2-methylpyridine, 3-methylpyridine, 2-chloropyridine, 2-fluoropyridine, 2-bromopyridine, 3-bromopyridine, 2,3-dichloropyridine, 4-chloropyrimidine, 2-chlorothiazole, 3-
20 methylisoxazole and the like.

The groups represented by "B¹" and "B²" in the compound of formula (I) are hydrogen atom, alkyl group or hydroxyl group; or combined together to represent carbonyl group. Preferable examples of alkyl group include C₁-C₄ lower alkyl such as methyl,
25 ethyl, propyl, isopropyl, butyl, sec-butyl and the like.

The dotted line in the compound of formula (I) shows either presence or absence of bond, and has following meanings in relation to number "n"; that is, in the case number "n" is 1, double bond is located between carbon atom of heterocyclic ring
30 and exocyclic nitrogen atom, and so said nitrogen atom corresponds to imino group, and in another case number "n" is 2, double bond is located between carbon atom of heterocyclic ring

and "X" which refers carbon or nitrogen atom, and then exocyclic nitrogen atom corresponds to amino group as substituent of heterocyclic ring.

The group represented by "X" in the compound of formula
5 (I) stands for oxygen atom, sulfur atom, carbon atom or nitrogen atom, and the "X" is combined with "Y" to constitute the partial component represented by "-Y-X-", which has follow meanings.

(1) in the case of "X" is oxygen atom, the term "-Y-X-" is

-CH₂-CH₂-O- or -CH₂-CH₂-CH₂-O-;

10 (2) in the case of "X" is sulfur atom, the term "-Y-X-" is

-CH₂-CH₂-S- or -C(R¹)=C(R²)-S-,

(in which, R¹ and R² are hydrogen atom; halogen atom; optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group);

15 (3) in the case of "X" is carbon atom, the term "-Y-X-" is

-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH=C(R³)-C(R⁴)=CH- or
-N=C(R⁵)-C(R⁶)=CH- ,

(in which, R³, R⁴, R⁵ and R⁶ are hydrogen atom; halogen atom; optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group);

20 (4) in the case of "X" is nitrogen atom, the term "-Y-X-" is

-CH₂-CH₂-NH-, -CH₂-CH₂-CH₂-NH-, -C(R⁷)=C(R⁸)-N= or
-C(R⁹)=C(R¹⁰)-C(R¹¹)=N-

25 (in which, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are hydrogen atom; halogen atom; optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group),

and the like.

30 The term "halogen atom" represented by R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ may include fluorine, chlorine, bromine and iodine.

The term "optionally substituted alkyl group" may include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl and the like.

5 The term "optionally substituted aryl group" may be non-substituted phenyl group or phenyl group which is substituted by halogen atom, or C₁-C₄ lower alkyl such as methyl, ethyl and the like, and therefore, examples of substituted phenyl group may include methylphenyl, chlorophenyl, dichlorophenyl and the like.

10 The term "heterocyclic group" may be 5 or 6 membered heterocyclic group containing the same or different 1 to 3 hetero atom(s) such as sulfur, nitrogen, oxygen atom(s), and examples include thiophene, furan, pyran, pyrrole, pyrazole, pyridine, pyrimidine, pyrazine, pyridazine, imidazole, oxazole, isoxazole, thiazole, isothiazole, quinoline, isoquinoline, tetrahydro-
15 pyrimidine and the like.

Suitable substituent of substituted heterocyclic group may include C₁-C₄ lower alkyl, halogen atom and the like, and therefore, examples of said substituted heterocyclic group may be
20 2-methylpyridine, 3-methylpyridine, 2-chloropyridine, 2-fluoropyridine, 2-bromopyridine, 3-bromopyridine, 2,3-dichloropyridine, 4-chloropyrimidine, 2-chlorothiazole, 3-methylisoxazole and the like.

25 The following are examples of heterocyclic compounds of the formula (I).

2-imino-3-phenacylthiazolidine;
3-acetonyl-2-imino-2,3-dihydrothiazole;
1-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-1,2-dihydropyrimidine;
3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-4-methyl-2,3-
30 dihydrothiazole;
3-[2-(6-chloro-3-pyridyl)ethyl]-2-iminothiazolidine;
3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-5-methyl-2,3-

- dihydrothiazole;
2-amino-1-[2-(6-chloro-3-pyridyl)ethyl]imidazole;
1-(6-chloro-3-pyridyl)-2-(2-imino-3-thiazolidinyl)-1-ethanone;
1-(6-chloro-3-pyridyl)-2-(2-imino-3-thiazolidinyl)-1-ethanol;
5 3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-4,5-dimethyl-2,3-dihydrothiazole;
2-amino-1-[2-(6-methyl-3-pyridyl)ethyl]imidazole;
1-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-1,2,3,4,5,6-hexahydropyrimidine;
10 2-amino-1-[2-(5,6-dichloro-3-pyridyl)ethyl]imidazole;
2-amino-1-[2-(3-pyridyl)ethyl]imidazole;
6-chloro-2-[2-(6-chloro-3-pyridyl)ethyl]-3-imino-2,3-dihydropyridazine;
1-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-1,2-dihydropyridine;
15 2-amino-1-[2-(4-chlorophenyl)ethyl]imidazole;
3-[2-(6-chloro-3-pyridyl)propyl]-2-imino-2,3-dihydrothiazole;
2-amino-1-[2-(2-pyridyl)ethyl]imidazole;
2-amino-1-[2-(4-pyridyl)ethyl]imidazole;
2-amino-1-[2-(6-chloro-3-pyridyl)ethyl]-4,5-dimethylimidazole;
20 3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-2,3-dihydrothiazole;
2-amino-1-[2-(2-chloro-5-thiazolyl)ethyl]imidazole;
3-[2-(2-chloro-5-thiazolyl)ethyl]-2-imino-2,3-dihydrothiazole;
2-amino-1-[2-(5-bromo-3-pyridyl)ethyl]imidazole;
2-amino-1-[2-(4-hydroxyphenyl)ethyl]imidazole;
25 2-amino-1-[2-(5-methyl-3-pyridyl)ethyl]imidazole;
2-imino-3-[2-(5-methyl-3-pyridyl)ethyl]-2,3-dihydrothiazole;
2-amino-1-[2-(5-pyrimidyl)ethyl]imidazole;
2-amino-1-[2-(3-pyridazinyl)ethyl]imidazole;
2-amino-1-[2-(2-pyrazinyl)ethyl]imidazole;
30 2-amino-1-{2-[2-(4-hydroxyphenyl)thiophenyl]ethyl}imidazole;
2-amino-1-{2-[2-(4-methoxyphenyl)thiophenyl]ethyl}imidazole;
2-amino-1-[2-(4-pyridazinyl)ethyl]imidazole;

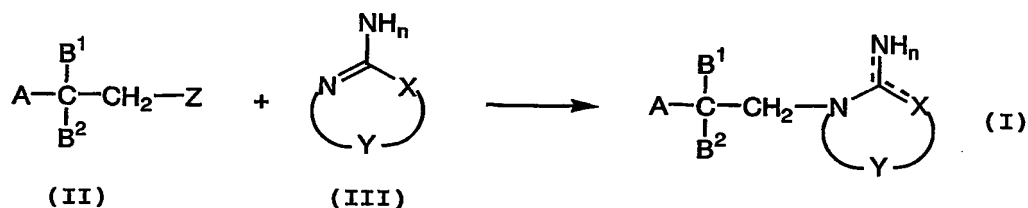
2-amino-1-[2-(4-chloro-5-pyrimidyl)ethyl]imidazole.

The heterocyclic compounds represented by the formula (I) of the present invention can be prepared in accordance with the various synthetic processes such as following Process 1 to 3.

In the following reaction schemes, the groups A, B¹, B², X, Y and n have the same meanings mentioned above.

Process 1:

In accordance with the following reaction scheme, the compound of the formula (II) is reacted with the compound of the formula (III) to obtain the compound (I) of the present invention.



wherein, "Z" is leaving group which accelerates the reaction with nitrogen atoms of heterocyclic ring, such as halogen atom, p-toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy, acyloxy, substituted acyloxy groups and so on.

The compound (III) to be used in this reaction can be commercially available or can be easily prepared from known compounds by using common methods.

The reaction of the compound (II) with the compound (III) to obtain the compound (I) can be usually carried out in an appropriate solvent such as alcohol solvent, ketone solvent, nitrile solvent, ester solvent, amide solvent, hydrocarbon solvent and ether solvent or the mixture thereof in the presence

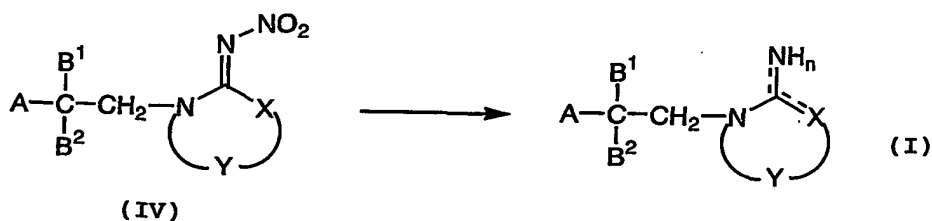
of an organic base or an inorganic base if necessary, under the temperature ranging from -20°C to the refluxing temperature of the solvent to be used.

The examples of alcohol solvent include methanol, ethanol, propanol, 2-propanol, 2-methyl-2-propanol and the like. The ketone solvent may include acetone, methyl ethyl ketone and the like. The nitrile solvent may include acetonitrile, propionitrile and so on, and the ester solvent may be ethyl acetate. The examples of amide solvent include N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, hexamethylphosphoramide and the like. The hydrocarbon solvent may include aromatic hydrocarbon such as benzene, toluene and the like, or aliphatic hydrocarbon such as pentane, hexane and the like. The examples of ether solvent may include diethyl ether, dimethoxyethane, tetrahydrofuran, 1,4-dioxane and the like.

Examples of the organic base to be used in the reaction may include triethylamine, collidine, lutidine, potassium tert-butoxide and the like, and the inorganic base may include potassium carbonate, sodium carbonate, sodium hydrogencarbonate, sodium hydroxide, potassium hydroxide and the like.

Process 2:

The compound (I) can be obtained by removing the nitro group of the compound (IV) in accordance with the following reaction scheme.



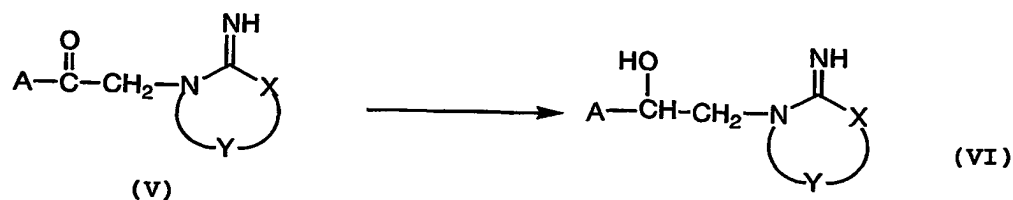
The compound (IV) to be used in this reaction can be prepared in accordance with the known method (Moriya K. et al., *J. Pesticides Sci.*, 18, 119-123 (1993)). Removing the nitro group of the compound (IV) can be conducted by using common method such as deprotection of peptides including nitroarginine.

This removing reaction of the nitro group of the compound (IV) can generally be carried out by treating with a reducing reagent in water, or in alcohol solvent, amide solvent, acid solvent alone, or in the mixture solvent thereof, at the temperature ranging from -20°C to 50°C, in the presence of an organic or an inorganic salt having buffer action, if necessary.

The examples of alcohol solvent include methanol, ethanol, propanol, 2-propanol, 2-methyl-2-propanol and the like. The amid solvent include N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, hexamethylphosphoramide and the like. The acid solvent may include formic acid, acetic acid, propionic acid, trifluoroacetic acid, hydrochloric acid and the like. The examples of the organic or inorganic salt having buffer action may include ammonium acetate, triethylamine, pyridine, phosphate salts and the like. The preferable reducing reagent is titanium(III) chloride.

Process 3:

The compound (I) can be obtained by the reduction of the compound (V) in accordance with the following reaction scheme.



This reaction can generally be carried out by treating

with a reducing reagent in water or alcohol solvent alone, or in the mixture solvent thereof, at the temperature ranging from -20°C to 50°C.

The examples of alcohol solvent include methanol, ethanol, 5 propanol, 2-propanol, 2-methyl-2-propanol and the like. The examples of reducing reagent include sodium borohydride, lithium borohydride, calcium borohydride, sodium trimethoxyborohydride, sodium cyanoborohydride and the like.

10 The compound of formula (I) of the present invention thus obtained can be converted to a pharmaceutically acceptable salt with various kinds of the organic or inorganic acids mentioned above, if necessary. Furthermore, the compound (I) of the present invention can also be purified by the conventional manner, such 15 as recrystallization, column chromatography and the like.

When the compounds of the formula (I) of the present invention exist in the isomer forms, each isomer *per se* is separated from each other by the conventional manner. Therefore, it is understood that each isomers *per se*, as well as the 20 isomeric mixture, shall be included in the compounds of the present invention.

The compounds of formula (I) of the present invention bind selectively to nicotinic acetylcholine receptors in central 25 nervous systems, and activate said receptors as agonists or modulators. Therefore, these compounds are useful as medicaments for preventing or treating various diseases, such as dementia, senile dementia, presenile dementia, Alzheimer's disease, Parkinson's disease, cerebrovascular dementia, AIDS-related 30 dementia, dementia in Down's syndrome, Tourette's syndrome, neurosis during chronic cerebral infarction stage, cerebral dysfunction caused by cerebral injury, anxiety, schizophrenia,

depression, Huntington's disease, pain and so on.

The compounds of formula (I) or a pharmaceutically acceptable salt thereof according to the present invention may be administered in the form of oral or parenteral formulations. The formulations for oral administration may include for example, tablets, capsules, granules, fine powders, syrups or the like; the formulations for parenteral administration may include, for example, injectable solutions or suspensions with distilled water for injection or other pharmaceutically acceptable solution, patches for transdermal application, sprays for nasally administration, depositories or the like.

These formulations may be formed by mixing with pharmaceutically acceptable carrier, excipient, sweetener, stabilizer and so on by the conventional procedures known *per se* to those skilled in the art in the field of pharmaceutical formulations.

Examples of pharmaceutically acceptable carrier or excipient include polyvinyl pyrrolidone, gum arabic, gelatin, sorbit, cyclodextrin, magnesium stearate, talc, polyethylene glycol, polyvinyl alcohol, silica, lactose, crystalline cellulose, sugar, starch, calcium phosphate, vegetable oil, carboxymethyl-cellulose, hydroxypropylcellulose, sodium lauryl sulfate, water, ethanol, glycerol, mannitol, syrup and the like.

The solutions for injection may be isotonic solution containing glucose and the like, and these solutions can be further contain an appropriate solubilizer such as polyethylene glycol or the like, buffer, stabilizer, preservative, antioxidant and so on.

These formulations can be administered to the human being and other mammalian animals, and the preferable administration route may include oral route, transdermic route, nasal route, rectal route, topical route or the like.

The administration dose may vary in a wide range with ages, weights, condition of patients, routes of administration or the like, and a usual recommended daily dose to adult patients for oral administration is within the range of approximately 0.001-1,000 mg/kg per body weight, preferably 0.01-100 mg/kg per body weight, and more preferably 0.1-10 mg/kg per body weight.

In the case of parenteral administration such as intravenous injections, a usual recommended daily dose is within the range of approximately 0.00001-10 mg/kg per body weight, preferably 0.0001-1 mg/kg per body weight, and more preferably 0.001-0.1 mg/kg per body weight, once or in three times per day.

The methods for evaluating the binding capabilities of the compounds at nicotinic acetylcholine receptors are different by subtypes of receptors. The binding capabilities of the compounds at $\alpha 4 \beta 2$ nicotinic acetylcholine receptors are examined using rat brain membrane obtained from whole homogenized brain, and determining the inhibiting rate of the compounds against [^3H]-cytisine binding to said brain membrane. Furthermore, the binding capabilities of the compounds at $\alpha 1 \beta 1 \gamma \delta$ nicotinic acetylcholine receptors are examined using homogenized rat muscle, and determining the inhibiting rate of the compounds against [^3H]- α -bungarotoxin binding to said muscle homogenate.

The agonist effect in human $\alpha 4 \beta 2$ subtype of nicotinic acetylcholine receptors are examined by using human nicotinic acetylcholine receptors prepared in oocytes of *Xenopus laevis*, which is injected with cRNA from the corresponding cloning cDNA of human $\alpha 4$ and $\beta 2$ subunits of nicotinic acetylcholine receptors, and to measure the expression of the electric response by adding the test compounds to perfusion solution by means of membrane potential holding method.

Examples:

The present invention is illustrated in more detail by way of the following examples.

5 Example 1: Synthesis by the Process 1**3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-5-methyl-2,3-dihydro-thiazole [Compound 6]**

10 A mixture of 440 mg (2 mmol) of 2-amino-5-methyl-2-thiazoline and 228 mg (2 mmol) of 5-(2-bromoethyl)-2-chloropyridine in 5 ml of acetonitrile was heated for 14 hours at 90°C under refluxing. Then, the reaction mixture was cooled to the room temperature, and the solvent was removed under reduced pressure. The resulting residue was treated with methanol and acetone and the precipitates were collected by filtration. The
15 obtained precipitate was purified by aminopropyl-coated silica gel (Chromatorex NH-type; Fuji Silysia Chemical Ltd.) column chromatography (eluent; dichloromethane) to give 310 mg (yield; 61.2%) of 3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-5-methyl-2,3-dihydrothiazole as colorless oil. This product was dissolved in
20 methanol and to this solution was added 130 mg (1.12 mmol) of fumaric acid, and the mixture was concentrated under reduced pressure. The resulting oily residue was treated with acetone to give crystalline. The crystalline was collected by filtration and dried in vacuum to give 392 mg of fumarate of the title Compound
25 6.

The following compounds were synthesized in accordance with the same procedures as described in Example 1.

Compound 1: 2-imino-3-phenacylthiazolidine;

30 Compound 2: 3-acetonyl-2-imino-2,3-dihydrothiazole;

Compound 3: 1-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-1,2-dihydropyrimidine;

Compound 4: 3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-4-methyl-2,3-dihydrothiazole;

Compound 5: 3-[2-(6-chloro-3-pyridyl)ethyl]-2-iminothiazolidine;

Compound 7: 2-amino-1-[2-(6-chloro-pyridyl)ethyl]imidazole;

5 Compound 8: 1-(6-chloro-3-pyridyl)-2-(2-imino-3-thiazolidinyl)-1-ethanone;

Compound 10: 3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-4,5-dimethyl-2,3-dihydrothiazole;

Compound 11: 2-amino-1-[2-(6-methyl-3-pyridyl)ethyl]imidazole;

10 Compound 13: 2-amino-1-[2-(5,6-dichloro-3-pyridyl)ethyl]-imidazole;

Compound 14: 2-amino-1-[2-(3-pyridyl)ethyl]imidazole;

Compound 15: 6-chloro-2-[2-(6-chloro-3-pyridyl)ethyl]-3-imino-2,3-dihydropyridazine;

15 Compound 16: 1-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-1,2-dihydropyridine;

Compound 17: 2-amino-1-[2-(4-chlorophenyl)ethyl]imidazole;

Compound 18: 3-[2-(6-chloro-3-pyridyl)propyl]-2-imino-2,3-dihydrothiazole;

20 Compound 19: 2-amino-1-[2-(2-pyridyl)ethyl]imidazole;

Compound 20: 2-amino-1-[2-(4-pyridyl)ethyl]imidazole;

Compound 21: 2-amino-1-[2-(6-chloro-3-pyridyl)ethyl]-4,5-dimethylimidazole;

25 Compound 22: 3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-2,3-dihydrothiazole;

Compound 23: 2-amino-1-[2-(2-chloro-5-thiazolyl)ethyl]imidazole;

Compound 24: 3-[2-(2-chloro-5-thiazolyl)ethyl]-2-imino-2,3-dihydrothiazole;

Compound 25: 2-amino-1-[2-(5-bromo-3-pyridyl)ethyl]imidazole;

30 Compound 26: 2-amino-1-[2-(4-hydroxyphenyl)ethyl]imidazole;

Compound 27: 2-amino-1-[2-(5-methyl-3-pyridyl)ethyl]imidazole;

Compound 28: 2-imino-3-[2-(5-methyl-3-pyridyl)ethyl]-2,3-

dihydrothiazole;

Compound 29: 2-amino-1-[2-(5-pyrimidyl)ethyl]imidazole;

Compound 30: 2-amino-1-[2-(3-pyridazinyl)ethyl]imidazole;

Compound 31: 2-amino-1-[2-(2-pyrazinyl)ethyl]imidazole;

5 Compound 32: 2-amino-1-{2-[2-(4-hydroxyphenyl)thiophenyl]ethyl}-
imidazole;

Compound 33: 2-amino-1-{2-[2-(4-methoxyphenyl)thiophenyl]ethyl}-
imidazole;

Compound 34: 2-amino-1-[2-(4-pyridazinyl)ethyl]imidazole;

10 Compound 35: 2-amino-1-[2-(4-chloro-5-pyrimidyl)ethyl]imidazole.

Example 2: Synthesis by the Process 2

1-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-1,2,3,4,5,6-hexahydro-
pyrimidine [Compound 12]

15 To a suspension of 112 mg (0.395 mmol) of 1-[2-(6-chloro-
3-pyridyl)ethyl]-2-nitroimino-1,2,3,4,5,6-hexahydropyrimidine in
6 ml of methanol were added 3.64 ml (14.6 mmol) of 4M ammonium
acetate and 1.82 ml of 20% titanium(III) chloride, and the
mixture was stirred for 1 hour at room temperature under nitrogen
20 atmosphere. Then, the solvent was removed under reduced pressure,
and 50% sodium hydroxide aqueous solution was added to the
resulting residue under ice-cooling. The insoluble matter was
removed off by filtration using Celite, and the filtrate was
concentrated under reduced pressure. The resulting residue was
25 purified by aminopropyl-coated silica gel (Chromatorex NH-type;
Fuji Silysia Chemical Ltd.) column chromatography (eluent;
dichloromethane, then dichloromethane : methanol = 5:1) to give
73 mg (yield; 77.5%) of 1-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-
1,2,3,4,5,6-hexahydropyrimidine as colorless oil. This product
30 was dissolved in methanol and to this solution was added 35 mg
(0.302 mmol) of fumaric acid, and the mixture was concentrated
under reduced pressure. The resulting oily residue was treated

with acetone to give crystalline. The crystalline was collected by filtration and dried in vacuum to give 24 mg of fumarate of the title Compound 12.

5 Example 3: Synthesis by the Process 3

1-(6-Chloro-3-pyridyl)-2-(2-imino-3-thiazolidinyl)-1-ethanol
[Compound 9]

To a suspension of 128 mg (0.5 mmol) of 1-(6-chloro-3-pyridyl)-2-(2-imino-3-thiazolidinyl)-1-ethanone in 5 ml of 2-
10 propanol was added 30 mg (0.793 mmol) of sodium borohydride, and the suspension was stirred for 30 minutes at room temperature. Then, the solvent was removed under reduced pressure and the resulting residue was mixed with dichloromethane and water, and the organic layer was separated. The organic layer was dried over
15 sodium sulfate, and the solvent was removed under reduced pressure to give 17 mg (yield; 13.2%) of 1-(6-chloro-3-pyridyl)-2-(2-imino-3-thiazolidinyl)-1-ethanol as colorless oil. This product was dissolved in methanol and to this solution was added 8 mg (0.069 mmol) of fumaric acid, and the mixture was
20 concentrated under reduced pressure. The resulting residue was treated with acetone to give crystalline. The crystalline was collected by filtration and dried in vacuum to give 12 mg of fumarate of the title Compound 9.

25 The physicochemical data of the compound obtained by the above-mentioned examples are summarized in the following Table 1 to Table 7.

TABLE 1:

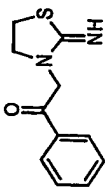
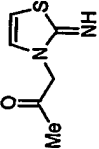
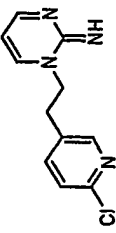
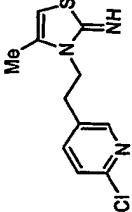
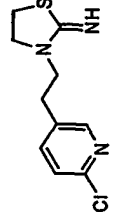
| No. | Chemical Structure | Salt | Properties m.p.(°C) crystallized solvent | Mass Spectrum found molecular formula | ¹ H-NMR(DMSO-d ₆) |
|-----|---|--------------|--|--|---|
| 1 |  | hydrobromide | colorless cryst. 173-175°C acetonitrile | m/z 221 = (M+H) ⁺ C ₁₁ H ₁₂ N ₂ OS | 9.52 (br, 2H), 7.98 (d, J=8.0Hz, 2H), 7.73 (t, J=7.4Hz, 1H), 7.60 (dd, J=7.4, 8.0Hz, 2H), 5.33 (s, 2H), 4.02 (t, J=7.6Hz, 2H), 3.58 (t, J=7.6Hz, 2H) |
| 2 |  | fumarate | colorless cryst. 122-124°C acetonitrile | m/z 139 = (M+H-H ₂ O) ⁺ C ₆ H ₈ N ₂ OS | 13.1 (br, 1H), 7.80 (d, J=4.4Hz, 1H), 7.46 (s, 1H), 7.14 (d, J=4.4Hz, 1H), 6.63 (s, 2H), 2.22 (s, 3H) |
| 3 |  | fumarate | yellow cryst. 190-192°C acetone | m/z 235 = (M+H) ⁺ C ₁₁ H ₁₁ ClN ₄ | 8.73 (m, 1H), 8.32 (s, 1H), 8.30 (d, J=8.2Hz, 1H), 7.82 (d, J=8.0Hz, 1H), 7.49 (d, J=8.0Hz, 1H), 6.89 (m, 1H), 6.42 (s, 2H), 4.37 (t, J=7.3Hz, 2H), 3.09 (t, J=7.3Hz, 2H) |
| 4 |  | fumarate | yellow cryst. 180-202°C acetone | m/z 254 = (M+H) ⁺ C ₁₁ H ₁₂ ClN ₃ S | 8.26 (d, J=2.2Hz, 1H), 7.74 (dd, J=2.2, 8.2Hz, 1H), 7.47 (d, J=8.2Hz, 1H), 6.52 (s, 2H), 6.02 (s, 1H), 3.97 (t, J=7.3Hz, 2H), 2.95 (t, J=7.3Hz, 2H), 1.96 (s, 3H) |
| 5 |  | fumarate | yellow cryst. 186-192°C acetone | m/z 242 = (M+H) ⁺ C ₁₀ H ₁₂ ClN ₃ S | 8.33 (d, J=2.2Hz, 1H), 7.80 (dd, J=2.2, 8.2Hz, 1H), 7.46 (d, J=8.2Hz, 1H), 6.48 (s, 2H), 3.76 (t, J=7.2Hz, 2H), 3.64 (t, J=7.3Hz, 2H), 3.27 (t, J=7.2Hz, 2H), 2.89 (t, J=7.3Hz, 2H) |

TABLE 2:

| No. | Chemical Structure | Salt | Properties m.p. (°C) crystallized solvent | Mass Spectrum found molecular formula | ¹ H-NMR (DMSO-d ₆) |
|-----|--------------------|----------------------------|---|---|---|
| 6 | | fumarate | pale brown cryst. 189-192°C acetone | m/z 254 = (M+H) ⁺ C ₁₁ H ₁₂ ClN ₃ S | 8.27 (d, J=2.2Hz, 1H), 7.75 (dd, J=2.2, 8.2Hz, 1H), 7.46 (d, J=8.2Hz, 1H), 6.76 (s, 1H), 6.51 (s, 2H), 4.02 (t, J=7.3Hz, 2H), 2.98 (t, J=7.3Hz, 2H), 2.07 (s, 3H) |
| 7 | | fumarate | pale yellow cryst. 186-188°C acetone | m/z 223 = (M+H) ⁺ C ₁₀ H ₁₁ ClN ₄ | 8.25 (d, J=2.4Hz, 1H), 7.72 (dd, J=2.4, 8.2Hz, 1H), 7.46 (d, J=8.2Hz, 1H), 7.18 (br, 2H), 6.72 (d, J=2.1Hz, 1H), 6.68 (d, J=2.1Hz, 1H), 6.52 (s, 2H), 4.02 (t, J=7.3Hz, 2H), 2.98 (t, J=7.3Hz, 2H) |
| 8 | | fumarate | colorless cryst. 145-162°C acetone | m/z 256 = (M+H) ⁺ C ₁₀ H ₁₀ ClN ₃ OS | 8.96 (s, 1H), 8.34 (d, J=7.2Hz, 1H), 7.65 (d, J=7.2Hz, 1H), 6.67 (s, 2H), 4.12 (s, 2H), 3.63 (t, J=7.5Hz, 2H), 3.31 (t, J=7.5Hz, 2H) |
| 9 | | fumarate | colorless cryst. 164-167°C acetone | m/z 258 = (M+H) ⁺ C ₁₀ H ₁₂ ClN ₃ OS | 8.44 (d, J=2.3Hz, 1H), 7.89 (dd, J=2.3, 8.2Hz, 1H), 7.51 (d, J=8.2Hz, 1H), 6.48 (s, 2H), 4.97 (m, 1H), 3.83 (t, J=7.2Hz, 2H), 3.62 (m, 2H), 3.30 (t, J=7.2Hz, 2H) |
| 10 | | fumarate (1/2 molecule) | pale yellow cryst. 213-216°C acetone | m/z 268 = (M+H) ⁺ C ₁₂ H ₁₄ ClN ₃ S | 8.31 (d, J=2.4Hz, 1H), 7.79 (dd, J=2.4, 8.2Hz, 1H), 7.49 (d, J=8.2Hz, 1H), 6.54 (s, 1H), 4.09 (t, J=7.7Hz, 2H), 2.97 (t, J=7.7Hz, 2H), 2.11 (s, 3H), 2.04 (s, 3H) |

TABLE 3:

| No. | Chemical Structure | Salt | Properties m.p. (°C) crystallized solvent | Mass Spectrum found molecular formula | ¹ H-NMR (DMSO-d ₆) |
|-----|--------------------|----------|---|--|--|
| 11 | | fumarate | pale yellow cryst. 170-171°C acetone | m/z 203 = (M+H) ⁺ C ₁₁ H ₁₄ N ₄ | 8.29 (d, J=2.0Hz, 1H), 7.77 (br, 2H), 7.54 (dd, J=2.0, 7.9Hz, 1H), 7.18 (d, J=7.9Hz, 1H), 6.81 (d, J=2.1Hz, 1H), 6.80 (d, J=2.1Hz, 1H), 6.53 (s, 2H), 4.02 (t, J=7.3Hz, 2H), 2.94 (t, J=7.3Hz, 2H), 2.42 (s, 3H) |
| 12 | | fumarate | colorless cryst. 235-242°C acetone | m/z 239 = (M+H) ⁺ C ₁₁ H ₁₃ ClN ₄ | 8.31 (s, 1H), 7.79 (d, J=8.0Hz, 1H), 7.43 (d, J=8.0Hz, 1H), 6.66 (s, 2H), 3.60 (t, J=7.4Hz, 2H), 3.26-3.38 (m, 4H), 2.97 (t, J=7.4Hz, 2H), 1.95 (m, 2H) in CD ₃ OD |
| 13 | | fumarate | pale yellow cryst. 192-193°C acetone | m/z 258 = (M+H) ⁺ C ₁₀ H ₁₀ Cl ₂ N ₄ | 8.23 (d, J=1.9Hz, 1H), 8.08 (d, J=1.9Hz, 1H), 7.47 (br, 2H), 6.76 (d, J=1.9Hz, 1H), 6.74 (d, J=1.9Hz, 1H), 6.51 (s, 2H), 4.04 (t, J=7.3Hz, 2H), 3.02 (t, J=7.3Hz, 2H) |
| 14 | | fumarate | colorless cryst. 152-154°C acetone | m/z 189 = (M+H) ⁺ C ₁₀ H ₁₂ N ₄ | 8.44 (s, 2H), 7.65 (d, J=7.9Hz, 1H), 7.33 (m, 1H), 6.68 (m, 2H), 6.51 (s, 2H), 4.01 (t, J=8.2Hz, 2H), 3.32 (br, 2H), 2.97 (t, J=8.2Hz, 2H) |
| 15 | | fumarate | pale brown cryst. 209-210°C acetone | m/z 270 = (M+H) ⁺ C ₁₁ H ₁₀ Cl ₂ N ₄ | 8.28 (s, 1H), 7.80 (m, 2H), 7.56 (d, J=8.9Hz, 1H), 7.43 (d, J=8.9Hz, 1H), 6.88 (s, 2H), 4.50 (t, J=7.3Hz, 2H), 3.26 (t, J=7.3Hz, 2H) in CD ₃ OD |

TABLE 4:

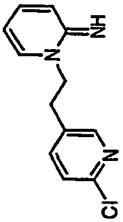
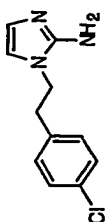
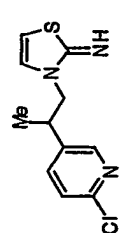
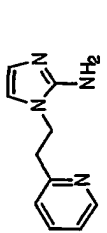
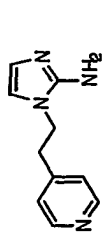
| No. | Chemical Structure | Salt | Properties m.p. (°C) crystallized solvent | Mass Spectrum found molecular formula | ¹ H-NMR (DMSO-d ₆) |
|-----|---|----------------------------|---|--|---|
| 16 |  | fumarate | pale brown cryst. 245–247°C acetone | m/z 234 = (M+H) ⁺ C ₁₂ H ₁₂ ClN ₃ | 8.31 (d, J=2.2Hz, 1H), 7.83 (m, 3H), 7.47 (d, J=8.5Hz, 1H), 7.17 (d, J=8.5Hz, 1H), 6.78 (t, J=8.8Hz, 1H), 6.40 (s, 2H), 4.45 (t, J=7.4Hz, 2H), 3.06 (t, J=7.4Hz, 2H) |
| 17 |  | fumarate (1/2 molecule) | colorless cryst. 186–188°C acetone | m/z 222 = (M+H) ⁺ C ₁₁ H ₁₂ ClN ₃ | 7.37 (d, J=8.2Hz, 2H), 7.27 (d, J=8.2Hz, 2H), 6.90 (br, 2H), 6.67 (s, 1H), 6.60 (s, 1H), 6.45 (s, 1H), 3.96 (t, J=7.5Hz, 2H), 2.93 (t, J=7.5Hz, 2H) |
| 18 |  | fumarate | colorless cryst. 182°C acetone | m/z 254 = (M+H) ⁺ C ₁₁ H ₁₂ ClN ₃ S | 8.19 (s, 1H), 7.77 (d, J=8.3Hz, 1H), 7.45 (d, J=8.3Hz, 1H), 7.08 (d, J=4.5Hz, 1H), 6.87 (d, J=4.5Hz, 1H), 6.68 (s, 2H), 4.29 (dd, J=6.9, 14.4Hz, 1H), 4.17 (dd, J=14.4, 9.3Hz, 1H), 3.31 (m, 1H), 1.40 (d, J=6.9Hz, 3H) in CD ₃ OD |
| 19 |  | fumarate | colorless cryst. 146–149°C acetone | m/z 189 = (M+H) ⁺ C ₁₀ H ₁₂ N ₄ | 8.52 (d, J=4.5Hz, 1H), 7.77 (t, J=7.6Hz, 1H), 7.30 (m, 2H), 6.75 (d, J=1.8Hz, 1H), 6.71 (d, J=1.8Hz, 1H), 6.69 (s, 2H), 4.24 (t, J=7.1Hz, 2H), 3.22 (t, J=7.1Hz, 2H) in CD ₃ OD |
| 20 |  | fumarate | colorless cryst. 180–181°C acetone | m/z 189 = (M+H) ⁺ C ₁₀ H ₁₂ N ₄ | 8.45 (d, J=5.6Hz, 2H), 7.30 (d, J=5.6Hz, 2H), 6.78 (d, J=2.4Hz, 1H), 6.75 (d, J=2.4Hz, 1H), 6.68 (s, 2H), 4.17 (t, J=7.1Hz, 2H), 3.12 (t, J=7.1Hz, 2H) in CD ₃ OD |

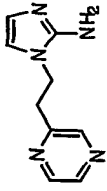
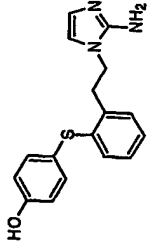
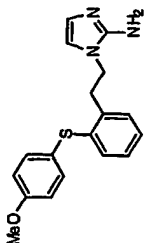

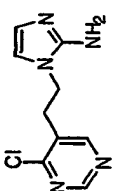
TABLE 5:

| No. | Chemical Structure | Salt | Properties m.p. (°C) crystallized solvent | Mass Spectrum found molecular formula | ¹ H-NMR (DMSO-d ₆) |
|-----|--------------------|----------|---|---|--|
| 21 | | fumarate | green cryst. 163-165°C acetone | m/z 251 = (M+H) ⁺ C ₁₂ H ₁₅ ClN ₄ | 8.15 (d, J=2.3Hz, 1H), 7.65(dd, J=2.3, 8.2Hz, 1H), 7.40 (d, J=8.2Hz, 1H), 6.68 (s, 2H), 4.05 (t, J=7.0Hz, 2H), 3.02 (t, J=7.0Hz, 2H), 2.05 (s, 3H), 1.93 (s, 3H) in CD ₃ OD |
| 22 | | fumarate | pale brown cryst. 204-205°C acetone | m/z 240 = (M+H) ⁺ C ₁₀ H ₁₀ ClN ₃ S | 8.20 (d, J=2.2Hz, 1H), 7.71 (dd, J=2.2, 8.2Hz, 1H), 7.41 (d, J=8.2Hz, 1H), 7.16 (d, 4.5Hz, 1H), 6.91 (d, J=4.5Hz, 1H), 6.68 (s, 2H), 4.30 (t, J=7.1Hz, 2H), 3.13 (t, J=7.1Hz, 2H) in CD ₃ OD |
| 23 | | fumarate | colorless cryst. 157-158°C acetone | m/z 229 = (M+H) ⁺ C ₈ H ₉ ClN ₄ S | 7.43 (s, 1H), 6.94 (br, 2H), 6.70 (d, J=1.7Hz, 1H), 6.66 (d, J=1.7Hz, 1H), 6.52 (s, 2H), 4.00 (t, J=7.1Hz, 2H), 3.20 (t, J=7.1Hz, 2H) |
| 24 | | fumarate | colorless cryst. 173-175°C acetone | m/z 246 = (M+H) ⁺ C ₈ H ₉ ClN ₃ S ₂ | 7.44 (s, 1H), 6.92 (d, J=4.8Hz, 1H), 6.55 (s, 2H), 6.33(d, J=4.8Hz, 1H), 4.03 (t, J=6.9Hz, 2H), 3.22 (t, J=6.9Hz, 2H) |
| 25 | | fumarate | pale yellow cryst. 167-168°C acetone | m/z 267 = (M+H) ⁺ C ₁₀ H ₁₁ BrN ₄ | 8.56 (s, 1H), 8.33 (s, 1H), 7.93 (s, 1H), 6.80 (s, 2H), 6.79 (s, 2H), 4.13 (t, J=7.1Hz, 2H), 3.10 (t, J=7.1Hz, 2H) in CD ₃ OD |

TABLE 6:

| No. | Chemical Structure | Salt | Properties m.p. (°C) crystallized solvent | Mass Spectrum found molecular formula | ¹ H-NMR (DMSO-d ₆) |
|-----|--------------------|--------------------------------|---|--|--|
| 26 | | fumarate | colorless cryst. 177-180°C acetone | m/z 204 = (M+H) ⁺ C ₁₁ H ₁₃ N ₃ O | 7.64 (br, 2H), 7.02 (d, J=8.2Hz, 2H), 6.75 (s, 2H), 6.67 (d, J=8.2Hz, 2H), 6.50 (s, 2H), 3.94 (t, J=7.4Hz, 2H), 2.83 (t, J=7.4Hz, 2H) |
| 27 | | fumarate | yellow cryst. 160-161°C acetone | m/z 203 = (M+H) ⁺ C ₁₁ H ₁₄ N ₄ | 8.28 (s, 1H), 8.24 (s, 1H), 7.56 (br, 2H), 7.49 (s, 1H), 6.78 (d, J=1.9Hz, 1H), 6.75 (d, J=1.9Hz, 1H), 6.51 (s, 2H), 4.02 (t, J=7.5Hz, 2H), 2.94 (t, J=7.5Hz, 2H), 2.27 (s, 3H) |
| 28 | | fumarate | colorless cryst. 191-192°C acetone | m/z 220 = (M+H) ⁺ C ₁₁ H ₁₃ N ₃ S | 8.28 (s, 1H), 8.23 (s, 1H), 7.49 (s, 1H), 6.98 (d, J=4.5Hz, 1H), 6.50 (s, 2H), 6.44 (d, J=4.5Hz, 1H), 4.07 (t, J=7.3Hz, 2H), 2.95 (t, J=7.3Hz, 2H), 2.26 (s, 3H) |
| 29 | | fumarate | yellow cryst. 167-168°C acetone | m/z 190 = (M+H) ⁺ C ₉ H ₁₁ N ₅ | 9.06 (s, 1H), 8.65 (s, 2H), 7.48 (br, 2H), 6.76 (s, 1H), 6.74 (s, 1H), 6.51 (s, 2H), 4.07 (t, J=7.2Hz, 2H), 3.01 (t, J=7.2Hz, 2H) |
| 30 | | hydrochloride (2 molecules) | yellow brown cryst. 190-198°C acetone | m/z 190 = (M+H) ⁺ C ₉ H ₁₁ N ₅ | 12.10 (s, 1H), 9.24 (d, J=4.3Hz, 1H), 7.90 (m, 2H), 7.82 (br, 2H), 6.94 (s, 1H), 6.87 (s, 1H), 4.38 (t, J=7.1Hz, 2H), 3.41 (t, J=7.1Hz, 2H) |

TABLE 7:

| No. | Chemical Structure | Salt | Properties m.p. (°C) crystallized solvent | Mass Spectrum found molecular formula | ¹ H-NMR (DMSO-d ₆) |
|-----|---|----------------------------|---|---|---|
| 31 |  | fumarate | yellow brown cryst. 147-149°C | m/z 190 = (M+H) ⁺ C ₈ H ₁₁ N ₅ | 8.58 (d, J=2.4Hz, 1H), 8.56 (s, 1H), 8.52 (d, J=2.4Hz, 1H), 7.48 (br, 2H), 6.72 (d, J=1.9Hz, 1H), 6.71 (d, J=1.9Hz, 1H), 6.51 (s, 2H), 4.20 (t, J=7.2Hz, 2H), 3.21 (t, J=7.2Hz, 2H) |
| 32 |  | fumarate (1/2 molecule) | colorless cryst. 218-219°C | m/z 312 = (M+H) ⁺ C ₁₇ H ₁₇ N ₃ OS | 7.24 (d, J=8.6Hz, 2H), 7.23 (s, 1H), 7.14 (m, 2H), 6.90 (m, 1H), 6.82 (d, J=8.6Hz, 2H), 6.55 (d, J=1.6Hz, 1H), 6.51 (d, J=1.6Hz, 1H), 6.48 (s, 1H), 6.40 (br, 2H), 3.97 (t, J=7.4Hz, 2H), 3.06 (t, J=7.4Hz, 2H) |
| 33 |  | fumarate (1/2 molecule) | colorless cryst. 153-156°C | m/z 326 = (M+H) ⁺ C ₁₈ H ₁₉ N ₃ OS | 7.32 (d, J=8.7Hz, 2H), 7.27 (m, 1H), 7.18 (m, 2H), 6.99 (d, 8.7Hz, 2H), 6.96 (m, 1H), 6.83 (br, 2H), 6.83 (d, J=1.8Hz, 1H), 6.54 (d, J=1.8Hz, 1H), 6.50 (s, 1H), 4.01 (t, J=7.4Hz, 2H), 3.77 (s, 3H), 3.08 (t, J=7.4Hz, 2H) |
| 34 |  | fumarate | yellow brown cryst. 162-163°C | m/z 190 = (M+H) ⁺ C ₉ H ₁₁ N ₅ | 9.13 (m, 2H), 7.54 (m, 1H), 7.30 (br, 2H), 6.74 (d, J=1.8Hz, 1H), 6.70 (d, J=1.8Hz, 1H), 6.51 (s, 2H), 4.09 (t, J=7.3Hz, 2H), 3.03 (t, J=7.3Hz, 2H) |
| 35 |  | fumarate | pale brown cryst. 146-149°C | m/z 224 = (M+H) ⁺ C ₉ H ₁₀ ClN ₅ | 8.93 (s, 1H), 8.64 (s, 1H), 6.97 (br, 2H), 6.63 (s, 2H), 6.52 (s, 2H), 4.09 (t, J=6.7Hz, 2H), 3.09 (t, J=6.7Hz, 2H) |

The effect of the compounds (I) of the present invention was evaluated by the following biological experiments.

Biological Experiment 1:

5 Binding assays at $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors

The affinity of the compounds of the present invention to $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors was performed by the following method, which was modified method described by
10 Pabreza L. A., Dhawan S. & Kellar K. J., *Mol. Pharm.*, 39, 9-12 (1990), and by Anderson D. J. & Arneric S. P., *Eur. J. Pharm.*, 253, 261-267 (1994).

(1) Preparation of rat brain membrane containing $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors

15 Fischer-344 strain male rats (body weight: 200-240 g; 9 weeks old) obtained from Charles River Japan were used. Rats were housed in the breeding cage controlled of the room temperature at $23 \pm 1^\circ\text{C}$, and the humidity of $55 \pm 5\%$ for 1 to 4 weeks. Rats (3 to 4 rats per a cage) were housed with lights on for 12 hours
20 daily (from 7:00 to 19:00), and allowed free access to food and water.

Preparation of rat brain membrane containing $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors was performed as follow. That is, rat brains were isolated just after sacrificed by
25 decapitation, washed with ice-cooled saline solution and then frozen at -80°C with liquid nitrogen and stored till using. After thawing the frozen brain, the brain was homogenized in 10 volumes of ice-cooled buffer solution (50 mM of Tris-HCl, 120 mM of NaCl, 5 mM of KCl, 1 mM of MgCl_2 , 2mM of CaCl_2 ; pH 7.4; 4°C) using
30 homogenizer (HG30, Hitachi Kohki Ltd.) for 30 seconds, and the homogenate were centrifuged under 1,000 x G for 10 minutes at 4°C . The resulting supernatant was separated and the pellet was

homogenized again with half volume of aforementioned prior buffer solution and centrifuged under the same conditions. Combined supernatant was further centrifuged under 40,000 x G for 20 minutes at 4°C. The pellet was suspended in buffer solution and
5 used for binding assays at receptors.

(2) Experiments of $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors binding

Suspensions of membrane pellets containing 400-600 μ g of
10 protein were added to test tubes containing test compounds and [³H]-cytisine (2 nM) in a final volume of 200 μ l and incubated for 75 minutes in ice-cooled bath. The samples were isolated by vacuum filtration onto Whatman GF/B filters, which were prerinsed with 0.5% polyethylenimine just prior to sample filtration, using
15 Brandel multi manifold cell harvester. The filters were rapidly washed with buffer solution (3 x 1 ml). The filters were counted in 3 ml of clearsol I (Nacalai Tesque Inc.). The determination of nonspecific binding was incubated in the presence of 10 μ M (-)-nicotine.

20 The analyses of the experimental results were conducted by using the Accufit Competition Program (Beckman Ltd.).

Biological Experiment 2:

25 Binding assays at $\alpha 1\beta 1\gamma \delta$ subtype of nicotinic acetylcholine receptors

The affinity of the compounds of the present invention to $\alpha 1\beta 1\gamma \delta$ subtype of nicotinic acetylcholine receptors was measured by the following method, which was modified method described by Garcha H. S., Thomas P., Spivak C. E., Wonnacott S. & Stoleran I.
30 P., *Psychopharmacology*, 110, 347-354 (1993).

(1) Preparation of rat skeletal muscles containing $\alpha 1\beta 1\gamma \delta$ subtype of nicotinic acetylcholine receptors

The substantially same animals described in the Biological Experiment 1 were used.

The isolation of $\alpha 1\beta 1\gamma\delta$ subtype of nicotinic acetylcholine receptors was performed as follow. That is, rat posterior skeletal muscles were isolated just after sacrificed by decapitation, washed with ice-cooled saline solution and then frozen at -80°C with liquid nitrogen and stored till using. After thawing the frozen muscles, tissue was homogenized (40% w/v) with buffer solution [2.5 mM of sodium phosphate buffer (pH:7.2), 90 mM of NaCl, 2 mM of KCl, 1 mM of EDTA, 2 mM of benzamidine, 0.1 mM of benzethonium chloride, 0.1 mM of PMSF, 0.01% of sodium azide] in Waring blender (Waring blender 34BL97; WARING PRODUCTS DIVISION DYNAMICS CORPORATION OF AMERICA) for 60 seconds. The homogenate were centrifuged under $20,000 \times G$ for 60 minutes at 4°C . The supernatant was separated and the resulting pellet was added to the same buffer (1.5 ml/g wet weight), and homogenized under the same conditions. Triton X100 (2% w/v) was added and the mixture was stirred for 3 hours at 4°C . The centrifugation at $100,000 \times G$ for 60 minutes at 4°C yielded the rat muscle extract as supernatant. This was stored at 4°C for up to 4 weeks, and used for binding assays at receptors.

(2) Experiments of $\alpha 1\beta 1\gamma\delta$ subtype of nicotinic acetylcholine receptors binding

Receptors binding experiments were performed as follow. That is, the extract of rat muscle containing 600-900 μg of protein was added to test tubes containing test compounds and incubated for 15 minutes at 37°C . Then, to this mixture was added 1 nM of [^3H]- α -bungarotoxin (α -Bgt) and further incubated for 2 hours. Th samples were isolated by vacuum filtration onto Whatman GF/B filters, which were prerinsed with 0.5% polyethylenimine just prior to sample filtration, using Brandel

multi manifold cell harvester. The filters were rapidly rinsed with washing solution (10 mM of KH_2PO_4 , 150 mM of NaCl, pH 7.2, room temperature) (5 x 1 ml). The filters were counted in 3 ml of clearsol I (Nacalai Tesque Inc.). The determination of nonspecific binding was incubated in the presence of 1 μM α -Bgt. The solutions containing α -Bgt (labeled/non-labeled) were prepared by using buffer solution containing 0.25% of BSA. In the receptor binding experiments, said buffer solution was added for adjusting the final concentration of BSA to be 0.05%.

The analyses of the experimental results were conducted by the same way as described in the Biological Experiment 1.

Table 8 shows the results of receptor binding studies of the compounds of the present invention and (-)-nicotine as reference compound.

TABLE 8:

| Compound No. | Affinities for receptors Ki | |
|--------------|---------------------------------|--|
| | $\alpha 4\beta 2$ ^{*1} | $\alpha 1\beta 1\gamma\delta$ ^{**2} |
| 1 | (93%, 68%) | n.d. |
| 2 | (107%, 101%) | n.d. |
| 3 | (72%, 17%) | (72%, 39%) |
| 4 | 5.6 nM | 10 μ M |
| 5 | 4.8 nM | 34 μ M |
| 6 | (77%, 35%) | (82%, 61%) |
| 7 | 4.9 nM | 184 μ M |
| 8 | 62 nM | 1829 μ M |
| 9 | (97%, 43%) | (72%, 35%) |
| 10 | 51 nM | 215 μ M |
| 11 | 21 nM | 1150 μ M |
| 12 | 1.4 nM | 12 μ M |
| 13 | 3.1 nM | 40 μ M |
| 14 | 3.5 nM | 223 μ M |
| 15 | (60%, 12%) | (93%, 61%) |
| 16 | 61 nM | 227 μ M |
| 17 | (97%, 78%) | (83%, 67%) |
| 18 | 84 nM | 173 μ M |
| 19 | (103%, 106%) | (106%, 86%) |
| 20 | (97%, 95%) | (109%, 90%) |
| 21 | 97 nM | 175 μ M |
| 22 | 7.4 nM | 132 μ M |
| 23 | 8.5 nM | 44 μ M |
| 24 | 35 nM | 58 μ M |
| 25 | 2 nM | 36 μ M |
| 26 | (93%, 60%) | (81%, 50%) |
| 27 | 21 nM | 339 μ M |
| 28 | 27 nM | 94 μ M |
| 29 | 6.0 nM | 447 μ M |
| 30 | 40 nM | 80 μ M |
| 31 | (75%, 22%) | (110%, 53%) |
| 32 | (102%, 73%) | (107%, 81%) |
| 33 | (111%, 92%) | (119%, 85%) |
| 34 | 68 nM | 1266 μ M |
| 35 | (61%, 17%) | (87%, 49%) |
| Nicotine | 1.6 nM | 182 μ M |

*1: Values indicated in a parenthesis show control % of [³H]-cytisine binding at 1 μ M and 10 μ M of test compounds, respectively.

**2: Values indicated in a parenthesis show control % of [³H]- α -Bgt binding at 100 μ M and 1,000 μ M of test compounds.

n.d.: not determined.

Biological Experiment 3:

Agonist activities at human $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors

The agonist activities of the compounds of the present invention at human $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors was evaluated by the following method, which was modified method described by Papke R. L., Thinschmidt J. S., Moulton B. A., Meyer E. M. & Poirier A., *Br. J. Pharmacol.*, 120, 429-438 (1997).

(1) Preparation of cRNA of human $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors

The cloning of human nicotinic acetylcholine receptor (hnACh-R) $\alpha 4$ cDNA and hnACh-R $\beta 2$ cDNA were performed, in accordance with the conventional manners, by synthesizing the each DNA primers corresponding to the sequences of hnACh-R $\alpha 4$ cDNA and hnACh-R $\beta 2$ cDNA [Monteggia L. M. et al., *Gene*, 155, 189-193 (1995); and Anand R., & Lindstrom J., *Nucl. Acids Res.*, 18, 4272 (1990)], and obtained hnACh-R $\alpha 4$ cDNA and hnACh-R $\beta 2$ cDNA by polymerase chain reaction (PCR), respectively. The obtained hnACh-R $\alpha 4$ cDNA and hnACh-R $\beta 2$ cDNA were inserted to the cRNA expression vector (pSP64 polyA) having SP6 RNA promoter to construct hnACh-R $\alpha 4$ /pSP64 polyA and hnACh-R $\beta 2$ /pSP64 polyA, respectively. After cutting from expression vector by restriction enzyme (EcoRI), transcription was performed by affecting SP6 RNA polymerase in the presence of cap analogues to obtain hnACh-R $\alpha 4$

cRNA and hnACh-R $\beta 2$ cRNA, respectively.

(2) Expression of human $\alpha 4\beta 2$ subtype nicotinic acetylcholine receptors in *Xenopus* oocytes

5 Oocytes were purchased from Kitanihonseibutsukyohzai Co., Ltd., which were already enucleated from *Xenopus laevis*, and used in this experiment.

The oocytes were treated with collagenase (Sigma type I; 1 mg/ml) in calcium-free modified Birth's solution (88 mM of NaCl, 1 mM of KCl, 2.4 mM of NaHCO₃, 0.82 mM of MgSO₄, 15 mM of HEPES, pH 7.6) under gently stirring at room temperature for 90 minutes, and washed out the enzyme from the tissue. Then, oocytes were separated from ovarian follicle by tweezers, and isolated oocytes were placed in antibiotics containing modified Birth's solution
10 (88 mM of NaCl, 1 mM of KCl, 2.4 mM of NaHCO₃, 0.82 mM of MgSO₄, 15 mM of HEPES, pH 7.6, and 0.1 v/v% of mixture solution containing of penicillin and streptomycin for incubation; Sigma Co.). Thus treated oocytes were injected with 50 nl of adjusted cRNAs (1.0 mg/ml), that is, each 50 ng of hnACh-R $\alpha 4$ cRNA and
15 hnACh-R $\beta 2$ cRNA per 1 oocyte by using automatic injector (NANOJECT; DRUMMOND SCIENTIFIC CO.), and further incubated for 4-14 days at 19°C. In oocytes, heterogeneous quintuple [$(\alpha 4)_2(\beta 2)_3$] was composed by translation of injected cRNAs, and ion channel receptors were constructed on cell membrane.

25

(3) Agonist activities at human $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors

The recordings of responses at human $\alpha 4\beta 2$ subtype of nicotinic acetylcholine receptors by means of membrane potential
30 holding method were performed as follow. That is, oocytes were placed in recording chamber with a total volume of 50 μ l and were perfused with Ringer's solution (115 mM of NaCl, 2.5 mM of KCl,

1.8 mM of CaCl_2 , 10 mM of HEPES, pH 7.3) containing atropine (1 μM) under flow rate of 1 ml/min. The membrane electric potentials were held at -50 mV by mean of the two electric membranes potential holding method (CEZ-1250; Nihon Kohden Co.). Test compounds were added to the perfusion solution, and recorded the peak strength of induced inward current. In order to normalize the responses of test compounds, the responses with acetylcholine (Ach) were recorded before and after application of the test compounds. Generally in the oocytes just after isolated, the response of intrinsic muscarinic acetylcholine receptors, which is inward electric current caused by activation of calcium dependence chloride ion channels with increase of the intracellular calcium concentration by stimulation of receptors, is observed. However, the complete disappearances of these responses were confirmed when treated with collagenase or added 1 μM of atropine. Furthermore, the oocytes without injection of cRNAs showed no responses by Ach after treatment with collagenase. Therefore, the responses observed in oocytes with injection of hnACh-R $\alpha 4$ cRNA and hnACh-R $\beta 2$ cRNA, i.e., the inward current induced by the intracellular influx of sodium ion according to the stimulation of receptors, would be the freshly observed responses of human $\alpha 4\beta 2$ subtype nicotinic acetylcholine receptors.

Table 9 shows the results of the agonist activity test of the compounds in the present invention and (-)-nicotine as reference compound.

TABLE 9:

| Compound No. | Agonist activity (ED50) ^{*1} |
|--------------|---------------------------------------|
| 7 | 2.5 μ M |
| 11 | 7.5 μ M |
| 12 | (8%) |
| 13 | 2.4 μ M |
| 14 | 2.0 μ M |
| 23 | 13 μ M |
| 25 | 3.0 μ M |
| 27 | 6.2 μ M |
| 29 | 3.7 μ M |
| 30 | 46 μ M |
| 31 | (15%) |
| 34 | 170 μ M |
| nicotine | 11.4 μ M |

^{*1}: These data are shown in control % by response at 100 μ M of the test compounds, in comparison with the response at 10 μ M of acetylcholine (100%). Values indicated in a parenthesis show control % by response at 100 μ M of the test compounds.

The following are Formulation Examples of the compounds (I) or pharmaceutically acceptable salt thereof according to the present invention

Formulation Example 1 (Tablets):

| | |
|--|--------|
| Compound 7 (Fumarate) | 25 g |
| Lactose | 130 g |
| Crystalline cellulose | 20 g |
| Corn starch | 20 g |
| 3% aqueous solution of hydroxypropylmethyl-cellulose | 100 ml |
| Magnesium stearate | 2 g |

Fumarate of Compound 7, lactose, crystalline cellulose and corn starch were screened through a 60-mesh sieve, homogenized

and charged into a kneader. A 3% aqueous solution of hydroxypropylmethylcellulose was added to the homogeneous mixture and the mixture was further kneaded. The product was granulated by a 16-mesh sieve, dried in air at 50°C, and again granulated by a 16-mesh sieve. Magnesium stearate was added to the granule and mixed again. The mixture was tabletted to produce tablets weighing 200 mg each and having an 8 mm diameter.

Formulation Example 2 (Capsules):

| | | |
|----|------------------------|---------|
| 10 | Compound 13 (Fumarate) | 25.0 g |
| | Lactose | 125.0 g |
| | Corn starch | 48.5 g |
| | Magnesium stearate | 1.5 g |

The above components were finely pulverized and thoroughly mixed to produce a homogeneous mixture. The mixture was filled in gelatin capsules, 200 mg per capsule, to obtain capsules.

Formulation Example 3 (Injection):

The fumarate of Compound 29 was filled in an amount of 250 mg in a vial and mixed in situ with approximately 4-5 ml of injectable distilled water to make an injectable solution.

INDUSTRIAL APPLICABILITY

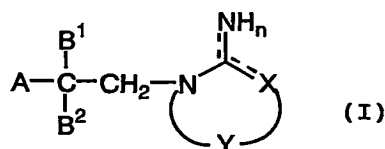
As described above, the compounds of the present invention possess high affinity for $\alpha 4\beta 2$ nicotinic acetylcholine receptor of central nervous systems and activate said $\alpha 4\beta 2$ nicotinic acetylcholine receptor as agonists or modulators. Therefore, the compounds of the present invention are useful for preventing or treating various kinds of diseases, which may be prevented or cured by activating nicotinic acetylcholine receptors.

Especially, the activators for $\alpha 4\beta 2$ nicotinic acetylcholine receptors of the present invention are useful for

preventing or treating various diseases such as dementia, senile dementia, presenile dementia, Alzheimer's disease, Parkinson's disease, cerebrovascular dementia, AIDS-related dementia, dementia in Down's syndrome, Tourette's syndrome, neurosis during
5 chronic cerebral infarction stage, cerebral dysfunction caused by cerebral injury, anxiety, schizophrenia, depression, Huntington's disease, pain and so on.

CLAIMS

1. Heterocyclic compounds represented by the following formula (I):



wherein:

A is optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group;

B¹ and B² are, hydrogen atom; alkyl group; or hydroxyl group; or combined together to represent carbonyl group;

X is oxygen atom; sulfur atom; carbon atom; or nitrogen atom;

dotted line shows either presence or absence of bond;

n is integer of 1 or 2; and

Y is,

(1) in the case of X is oxygen atom, group -Y-X- is -CH₂-CH₂-O- or -CH₂-CH₂-CH₂-O-;

(2) in the case of X is sulfur atom, group -Y-X- is -CH₂-CH₂-S- or -C(R¹)=C(R²)-S- (in which, R¹ and R² are hydrogen atom; halogen atom; optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group);

(3) in the case of X is carbon atom, group -Y-X- is -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH=C(R³)-C(R⁴)=CH- or -N=C(R⁵)-C(R⁶)=CH- (in which, R³, R⁴, R⁵ and R⁶ are hydrogen atom; halogen atom; optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group); and,

(4) in the case of X is nitrogen atom, group -Y-X- is -CH₂-CH₂-NH-, -CH₂-CH₂-CH₂-NH-, -C(R⁷)=C(R⁸)-N=, or -C(R⁹)=C(R¹⁰)-

$C(R^{11})=N-$ (in which, R^7 , R^8 , R^9 , R^{10} and R^{11} are hydrogen atom; halogen atom; optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group);

5 or pharmaceutically acceptable salts thereof.

2. The following compounds represented by the formula (I) of claim 1;

2-imino-3-phenacylthiazolidine;

10 3-acetonyl-2-imino-2,3-dihydrothiazole;

1-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-1,2-dihydropyrimidine;

3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-4-methyl-2,3-dihydrothiazole;

3-[2-(6-chloro-3-pyridyl)ethyl]-2-iminothiazolidine;

15 3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-5-methyl-2,3-dihydrothiazole;

2-amino-1-[2-(6-chloro-3-pyridyl)ethyl]imidazole;

1-(6-chloro-3-pyridyl)-2-(2-imino-3-thiazolidinyl)-1-ethanone;

1-(6-chloro-3-pyridyl)-2-(2-imino-3-thiazolidinyl)-1-ethanol;

20 3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-4,5-dimethyl-2,3-dihydrothiazole;

2-amino-1-[2-(6-methyl-3-pyridyl)ethyl]imidazole;

1-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-1,2,3,4,5,6-hexahydropyrimidine;

25 2-amino-1-[2-(5,6-dichloro-3-pyridyl)ethyl]imidazole;

2-amino-1-[2-(3-pyridyl)ethyl]imidazole;

6-chloro-2-[2-(6-chloro-3-pyridyl)ethyl]-3-imino-2,3-dihydropyridazine;

1-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-1,2-dihydropyridine;

30 2-amino-1-[2-(4-chlorophenyl)ethyl]imidazole;

3-[2-(6-chloro-3-pyridyl)propyl]-2-imino-2,3-dihydrothiazol ;

2-amino-1-[2-(2-pyridyl)ethyl]imidazole;

- 2-amino-1-[2-(4-pyridyl)ethyl]imidazole;
2-amino-1-[2-(6-chloro-3-pyridyl)ethyl]-4,5-dimethylimidazole;
3-[2-(6-chloro-3-pyridyl)ethyl]-2-imino-2,3-dihydrothiazole;
2-amino-1-[2-(2-chloro-5-thiazolyl)ethyl]imidazole;
5 3-[2-(2-chloro-5-thiazolyl)ethyl]-2-imino-2,3-dihydrothiazole;
2-amino-1-[2-(5-bromo-3-pyridyl)ethyl]imidazole;
2-amino-1-[2-(4-hydroxyphenyl)ethyl]imidazole;
2-amino-1-[2-(5-methyl-3-pyridyl)ethyl]imidazole;
2-imino-3-[2-(5-methyl-3-pyridyl)ethyl]-2,3-dihydrothiazole;
10 2-amino-1-[2-(5-pyrimidyl)ethyl]imidazole;
2-amino-1-[2-(3-pyridaziny]ethyl]imidazole;
2-amino-1-[2-(2-pyraziny]ethyl]imidazole;
2-amino-1-{2-[2-(4-hydroxyphenyl)thiophenyl]ethyl}imidazole;
2-amino-1-{2-[2-(4-methoxyphenyl)thiophenyl]ethyl}imidazole;
15 2-amino-1-[2-(4-pyridaziny]ethyl]imidazole;
2-amino-1-[2-(4-chloro-5-pyrimidyl)ethyl]imidazole.
and pharmaceutically acceptable salt thereof.

3. Activators for $\alpha 4\beta 2$ nicotinic acetylcholine receptors
20 containing the compound or pharmaceutically acceptable salt
thereof claimed in claim 1 or 2, as active ingredient.

4. The activators for $\alpha 4\beta 2$ nicotinic acetylcholine receptors
according to claim 3, wherein said activators are agonists or
25 modulators at $\alpha 4\beta 2$ nicotinic acetylcholine receptors.

5. A medicament for preventing or treating cerebral
circulation diseases comprising the activator for $\alpha 4\beta 2$ nicotinic
acetylcholine receptors claimed in claim 3 or 4.

30

6. A medicament for preventing or treating neurodegenerative
disease, dementia, motor ataxia, and neuropathy and mental

disease comprising the activator for $\alpha 4\beta 2$ nicotinic acetylcholine receptors claimed in claim 3 or 4.

7. The medicament according to claim 6, wherein said
5 neurodegenerative disease is Alzheimer's disease or Parkinson's disease, said dementia is cerebrovascular dementia, said motor ataxia is Tourette's syndrome, and said neuropathy and mental disease is neurosis during chronic cerebral infarction stage, anxiety or schizophrenia.

10

8. A medicament for improving the cerebral metabolism, neurotransmission functional disorder and memory disorder, for protecting brain, or having analgesic effect, which comprises the activator for $\alpha 4\beta 2$ nicotinic acetylcholine receptors claimed in
15 claim 3 or 4.

9. A medicament for preventing or treating inflammatory intestinal diseases comprising the activator for $\alpha 4\beta 2$ nicotinic acetylcholine receptors claimed in claim 3 or 4.

20

10. The use of the compounds claimed in claim 1 or 2 as the activators for $\alpha 4\beta 2$ nicotinic acetylcholine receptors.

11. The method of preventing or treating cerebral circulation
25 diseases which comprises administering activators for $\alpha 4\beta 2$ nicotinic acetylcholine receptors claimed in claim 3 or 4.

12. The method of preventing or treating neurodegenerative disease, dementia, motor ataxia, and neuropathy and mental
30 disease which comprises administering activators for $\alpha 4\beta 2$ nicotinic acetylcholine receptors claimed in claim 3 or 4.

13. The method according to claim 12, wherein said neuro-
degenerative disease is Alzheimer's disease or Parkinson's
disease, said dementia is cerebrovascular dementia, said motor
ataxia is Tourette's syndrome, and said neuropathy and mental
5 disease is neurosis during chronic cerebral infarction stage,
anxiety or schizophrenia.

INTERNATIONAL SEARCH REPORT

National Application No.
PC/JP 01/03377

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D277/18 C07D277/40 C07D401/06 C07D417/06 C07D213/73
 C07D233/88 C07D403/06 A61K31/426 A61K31/427 A61K31/505
 A61K31/506 A61K31/4164 A61K31/4178 A61K31/44 A61K31/4427

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, BEILSTEIN Data, CHEM ABS Data

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* Special categories of cited documents:

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- *Z* document member of the same patent family

Date of the actual completion of the international search

25 September 2001

Date of mailing of the international search report

09/10/2001

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INTERNATIONAL SEARCH REPORT

National Application No
PCT/JP 01/03377

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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- *Z* document member of the same patent family

Date of the actual completion of the international search

25 September 2001

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 01/03377

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International Application No
PCT/JP 01/03377

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